REMARKS

Claims 1-16 are pending in the present application.

Claims 7, 15 and 16 have been canceled. The specification has been amended to insert priority data as given on the Application Data Sheet. Claim 1 has been amended. Support for amended claims 1 is found in the specification, e.g., at page 8, lines 24-28; page 19, lines 22-32; and Examples 2-7. Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**".

Claims 1-16 stand rejected under 35 U.S.C. § 112, first paragraph.

The Examiner acknowledges that the specification is enabling for a method comprising administering an AAV vector comprising a nucleotide sequence encoding a marker protein operatively linked to a promoter into an artery following balloon catheter injury such that expression of the marker protein occurs in adventitial, microvascular endothelial cells.

The Examiner has raised several different arguments, which will be answered in turn.

• **(1)** The Examiner asserts that, "None of the claims require expression of a protein encoded by the AAV vector. Mere introduction of an AAV [sic, vector] into a blood vessel or cell does not have a use that is enabled in the specification or the art at the time of filing. What is required is expression of the protein."

Applicants respectfully disagree. Expression of a protein is not required for the methods of the invention as claimed to have utility. The products of exogenous nucleic acid introduced

into a cell include RNA and protein, as was understood by those of ordinary skill in the art at the time the application was filed. While proteins are acknowledged to have myriad uses, RNA also is useful, without the production of protein, for example, in the formation of ribozymes or as antisense RNA, as described in the instant application at, e.g., page 19, lines 17-21[1].

Claim 1 as amended recites that a product of the nucleic acid of the rAAV is made. The claims thus clearly set forth that introducing the rAAV vector results in product formation, for example, RNA or protein. The utility of either or both of these products is well-established, as discussed herein and in the art.

The Examiner has also stated that a promoter is essential to obtain protein expression because it cannot occur otherwise. Applicants respectfully submit that, as stated previously (Amendment filed June 29, 2000, p. 12), one of skill in the art at the time the application was filed was well aware of the necessity for a promoter to allow transcription of the polynucleotide. Furthermore, the vectors of the invention have been amply described and enabled to include a promoter in general and in numerous embodiments. See, e.g., instant application at page 6, lines 2-4 and 31-32; page 16, lines 11-14; and Example 1.

• **(2)** The Examiner asserts that, "Given the teachings of the art taken with the guidance of the specification it would require one of skill undue experimentation to obtain delivery or

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[1] Antisense RNA was discussed extensively as a useful product in the Amendment filed June 29, 2000 and during the Examiner's interview of December 9, 1999. As stated in the Amendment, pp. 6-7, ". . . Applicants respectfully submit that the specification also provides ample teachings to enable transduction of heterologous polynucleotides that are useful for non-therapeutic purposes. As the Primary Examiner (Ms. Chambers) acknowledged during the interview, non-limiting examples of non-therapeutic uses for transducing marker genes (including detectable and selectable ones) include diagnostic functions such as measuring trafficking of cellular or subcellular components associated with the marker gene expression in assessing plaque growth. As discussed, these non-therapeutic utilities are readily apparent to one skilled in the art. See specification at page 17, lines 9-16. The usefulness of expression of *non*-marker polynucleotides, such as those that encode antisense mRNA (as described in specification, page 19, lines 17-21), is also readily apparent to one of skill in the art. For example, they can be useful for various purposes including functioning as investigative tools to study biological processes and conferring upon a cell or tissue novel biological traits such as resistance to agents or processes to which the cell or tissue is normally susceptible. Thus, the specification also enables transduction for non-therapeutic uses which are encompassed by the scope of the claims." The Examiner has not responded on the record to these statments.

expression in microvessels, microvascular cells or the adventitia without a balloon catheter as broadly encompassed by the claims."

Applicants respectfully submit that the claims, which are directed to methods of transduction, are fully enabled by the originally filed specification. Applicants have described how to make the rAAV vectors for use in accordance with the claims and how to deliver those vectors to transduce cells in a blood vessel. See, for example, page 15, line 22 through page 16, line 10 for a description of making rAAV vectors, and page 19, lines 22-32, for a description of introduction of rAAV into blood vessels. Further, Applicants have exemplified transduction of blood vessel cells. Example 2 (2a-2g) exemplifies transduction of vascular smooth muscle cells and endothelial cells (both from large vessel and the microvasculature). Examples 4-7 exemplify transduction of endothelial cells.

In further support of Applicants' position, Applicants previously submitted the Declaration of Randolf L. Geary (Declaration of Randolph Geary pursuant to 37 C.F.R. § 1.132, mailed August 17, 1999, hereinafter the "Geary Declaration"). The Geary Declaration describes experiments in which an rAAV vector was used to transduce blood vessel cells in a primate model. ACAPSN (an rAAV vector carrying an expression construct for human alkaline phosphatase) was introduced into the lumen of monkey arteries for a 30 minute exposure. The arteries were not subject to pretreatment. Arteries were assayed for human alkaline phosphatase (hAP) activity at two, four, and eight weeks. hAP activity was detected in arteries from two of three test subjects. Summarizing the results presented in the Declaration, Dr. Geary states "[t]his experiment shows that significant transgene expression occurs and persists in medial smooth muscle cells following *in vivo* delivery of AAV to primate arteries." These experiments, using the techniques of the specification, show transduction and expression with no distension of the blood vessel.

The Examiner has responded by asserting that the declaration of Geary does not correlate with the specification because the dosages used in the Geary declaration were greater than those given in the Examples of the specification (Office Action, February 23, 2001). Applicants note that the specification states that "General techniques regarding delivery, frequency, composition and dosage ranges of vector solutions can be found in references such as those cited herein." Page 19, lines 14-16. Thus, the dosage to be used in the invention, as stated in the specification, would be the dosage that one of skill in the art, given the state of the art as exemplified by

references such as those cited, would use. At the time of the invention, vector dosage used was generally the highest obtainable, and were equivalent to those reported in the Geary declaration. See, e.g., a reference cited by the Examiner in the present Office action, Verma and Somia, *Nature* 389:239-242 (1997), which states: "Up to 10^{11}-10^{12} viral particles can be produced per ml . . ." Verma, page 241. See also, e.g., Maeda *et al.* Gene transfer into vascular cells using adeno-associated virus (AAV) vectors. Cardiovascular Research. 35:514-521 (1997), which reported using 10^{12} DNase-resistant particles (DRP) per ml in ex vivo gene transfer to rat aorta. This is comparable to the dosage of 250 ul of 4.5 X 10^{11} particles/ml (total dosage about 1.1 X 10^{11} particles) reported in the Geary Declaration.

In addition, dose and concentration are not always linked. In a small space (such as the inside of a small artery) the numbers of viral particles introduced is limited by concentration of virus stocks. In other applications where space is not an issue doses as high or higher than reported by the Geary Declaration could be achieved by simply increasing the volume. This was being done at the time of the present application. An example is delivery of AAV vectors to the lungs of animals where doses of 10^{11} particles were given in studies contemporary to those of the present application. See, e.g., Afione, S.A. *et al.* In vivo model of adeno-associated virus vector persistence and rescue. *Journal of Virology*, May 1996, pp 3235-3241. Others used concentrations similar to those cited in the Geary declaration.

Finally, the concentrations stated in the Geary Declaration refer to DNase-resistant particles (DRP) but the view of those of skill in the art was that only 1 of 1000 particles is actually infectious. See, e.g., Verma and Somia, p. 241: ". . .only one in 100-1,000 particles is infectious." So actual infectious particle titers in the studies reported in the Geary Declaration were ~1000 times lower than the concentrations Geary reports using (in DRP), and comparable to those of others who have reported their viral concentrations as "infectious particles per ml." See, e.g., Rolling *et al.*, Adeno-associated virus-mediated gene transfer into rat carotid arteries, *Gene Therapy* 4:757-761 (1997), where the authors used 10^{7} "infectious" particles per ml which would be equivalent to ~10^{10} DRP/ml.

Thus, as stated in the specification, dosages reported in "references such as those cited herein," and which were the choice of those of skill in the art, are dosages that are equivalent to those reported in the Geary Declaration, and the Examiner's assertion that such dosages are not

contemplated in the specification is incorrect. Such dosages are quite clearly contemplated in the specification.

• **(3)** The Examiner asserts that claims 4 and 16 require the AAV vector comprises a therapeutic gene, but do not require obtaining any therapeutic effect. "Mere introduction of an AAV comprising a therapeutic gene into a blood vessel or cell as claimed does not have a use that is enabled in the spec or the art at the time of filing . . . Furthermore, the specification does not enable one of skill to use the claimed invention to obtain a therapeutic effect [citing and discussing Miller, *FASEB J.* 9:190-199 (1995]; Deonarain, *Expert Opin. Ther. Pat.* 8:53-69 (1998); Verma, *Nature* 389:239-242 (1997); and Crystal, *Science* 270:404-410 (1995)]"

Claim 16 has been canceled.

Applicants respectfully traverse the rejection of claim 4.

Applicants note that claim 1 as amended requires that a product of the transduced gene be produced. Claim 4 depends from claim 1 and therefore requires that a product of the therapeutic gene be produced. The utility of the invention as claimed is as therapy; e.g., prophylaxis, cure, or other beneficial effect in an individual. See specification, page 7, lines 21-23: "A 'therapeutic polynucleotide' or 'therapeutic gene' refers to a nucleotide sequence that is capable, when transferred to an individual, of eliciting a prophylactic, curative, or other beneficial effect in the individual."

Regarding the Examiner's assertion that claim 4 is not enabled: For a *prima facie* case on non-enablement, the burden is on the Office to demonstrate that there is a reasonable basis to question the presumptively sufficient disclosure made by applicant. See, e.g., *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993); MPEP § 2164.04. In other words, the specification must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Furthermore, it is incumbent upon the Examiner to explain why one skilled in the art would doubt the truth or accuracy of any statement in a supporting disclosure and to back up these assertions with acceptable and specific

evidence. *Id.* at 370. Absent evidence to the contrary, the specification must be assumed to be enabling.

Applicants note that the Examiner has cited U.S. Patent 6,162,796 (Kaplitt *et al.*) as anticipating claim 4 of the instant application (see Office Action, page 8). Kaplitt *et al.* contains a single example, wherein a marker gene (for imaging) was introduced into the heart of a pig using an AAV vector. See Kaplitt *et al.*, col. 14, lines 32-51. If Kaplitt is enabled for therapeutic gene expression on the basis of marker gene expression, as it must be for the Examiner to use it as a reference under 35 U.S.C. § 102, then the claims to a therapeutic gene in the present application, which teaches marker gene transduction by use of an AAV vector, are also enabled. If marker gene expression does not enable therapeutic gene expression, then Kaplitt *et al.* is not enabled and may not be used as a reference under 35 U.S.C. § 102.

In addition, the Applicants have submitted declaratory evidence that correlates the level of expression of marker genes employed in the instant specification with a therapeutic effect. See declaration of Dr. Barrie Carter, submitted June 29, 2000. As noted in the Amendment of June 29, 2000,

> In view of the above, the Examiner bears the burden to show, with objective evidence, why he doubts this correlation. The law is clear that a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as satisfying the enablement requirement unless there is reason to doubt the objective truth of the teachings of the specification. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). It is incumbent upon the Examiner to explain why one skilled in the art would doubt the truth of statements made in the specification, and provide back up assertions with acceptable and specific evidence. *Id.* at 370. Absent evidence to the contrary, the specification must be assumed to be enabling. If the Examiner's assertion is based on personal knowledge, Applicants request that the Examiner submit an affidavit in accordance with 37 CFR §1.104(d)(2), which states that "[w]hen a rejection in an application is based on facts within the personal knowledge of an employee of the Office . . . the reference must be supported, when called for by the Applicant, by the affidavit of such employee . . ." (emphasis added). *See also In re Alton*, 37 USPQ.2d. 1578 (Fed. Cir. 1996), in which the Federal Circuit stated that an examiner cannot rebut a declaration with conclusory statements in

order to maintain a §112, ¶ 1 rejection. Maintaining this rejection in the absence of the requested evidence violates well-settled legal standards.

Applicants repeat their request that the Examiner provide objective evidence, or an affidavit as to his personal knowledge, for his assertion that the invention is not enabled, in the face of the specification as written and declaratory evidence.

Finally, the Examiner cites three publications that review various vectors known in the art (Miller and Vile, *FASEB J.* 9:190-199 (1997); Verma and Somia, *Nature* 389:239-242 (1997); and Crystal, *Science* 270:404-410 (1995); hereinafter "Miller," "Verma," and "Crystal," respectively) and one that indicates that "one of the biggest problems hampering successful gene therapy is the 'ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time.'" (Deonarain, *Exp. Opin. Ther. Patents* 8:53-69 (1998), hereinafter "Deonarian"). Office Action, page 5. The references cited by the Examiner not only do not argue against enablement of the use of AAV vectors to transfect blood vessel cells, they strengthen the case for enablement.

None of the publications are directed to the use of AAV vectors to transform blood vessel cells and are thus not relevant to the present invention. Indeed, only one of the cited references (Verma) even mentions AAV vectors in any context, and this reference reports the successful use of AAV as a vector for *in vivo* transfection of liver and muscle cells in immunocompetent mice, which produced "therapeutic amounts of factor IX protein in their blood for over six months." (Verma, p. 21). Not only do the other references Examiner not even mention the vectors used in the present application to transform blood vessel cells, but Deonarian states, "It is difficult to compare the efficiency of different gene delivery systems, especially between those that target different receptors as each delivery route is different." (Deonarian, p. 65). Thus, the references cited by the Examiner indicate that their conclusions concerning non-AAV vectors are not applicable to AAV vectors, and, further, the one reference that mentions AAV vectors indicates that they have had a successful therapeutic outcome.

Applicants also note that to support rejections under 35 U.S.C. 103 (a) the Examiner repeatedly invokes the principal of inherency, stating that, "Administering AAV after balloon catheter injury . . . inherently results in transduction of microvascular cells of the adventitia . . . because balloon catheter injury is the method used by applicants to obtain transduction of microvascular of the adventitia." (Office Action, p. 13) and further, "Nabel supports the inherency of transducing microvascular cells of the adventitia after balloon catheter injury." *Id.* Inherency requires that the process asserted to be inherent is something that must necessarily occur. The Examiner has therefore conceded that the process claimed by the Applicants necessarily must occur, at least in microvascular adventitia cells. Furthermore, the Examiner has stated that "Balloon catheter injury as taught by Branellec inherently results in proliferation of cells in the injured wall . . ." (Office Action, page 13). If this is the case, then at the very least, claims 10 and 11 of the present application, in which the transduced cell is a proliferating cell, must be enabled, by the Examiner's own arguments.

Applicants respectfully submit that the Examiner has not produced any evidence to establish that with the teachings in the specification, a person skilled in the art could not transduce a cell in a blood vessel by contacting the cell with a recombinant AAV vector comprising a therapeutic gene in vivo with a sufficient dosage and for a sufficient duration to transduce the cell. Art cited by the Examiner indicates that therapeutic outcomes have already been achieved with such vectors. Thus, the Office has failed to establish a *prima facie* case on non-enablement. Applicants' specification provides a presumptively sufficient disclosure providing ample teachings to allow a person skilled in the art to make and/or use the invention without undue experimentation.

Applicants respectfully submit that the presently claimed invention is in compliance with enablement requirements.

Claims 1-16 stand rejected under 35 U.S.C. § 112, second paragraph.

The Examiner has stated that claims 1-14 are indefinite because the preamble and the body of the claims are allegedly not commensurate in scope, that claim 1 is indefinite because it is allegedly unclear if the blood vessel in the body of the claim is the same as the blood vessel in which the cell is transduced, and that claim 5-7 are indefinite because it is allegedly unclear if "said blood vessel" refers to the blood vessel in the preamble or the blood vessel in the body of the claim. Claims 15 and 16 have been canceled.

Although Applicants maintain that the claims are definite as written, in order to expedite prosecution, and without acknowledging that the instant rejection has merit, claim 1 has been amended to recite, "A method of transducing a cell in a blood vessel of an individual, comprising contacting said cell with a recombinant adeno-associated viral (rAAV) vector in vivo at a sufficient dosage and for a sufficient duration to transduce said cell, whereby said cell is transduced." Support for this amendment is found in the specification as described above. The amended claim contains a limitation to transducing the blood vessel cell, so that the preamble and the body of the claim are commensurate. The amended claim recites the limitation of "a blood vessel" only once thus eliminating any putative lack of clarity concerning identity of the blood vessel, both in claim 1 and in claims 5-7.

Thus, the claims as amended are definite, and Applicants respectfully request that the rejection under 35 U.S.C. § 112, 2nd ¶, be withdrawn.

Claims 1-16 stand rejected under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 6,162,796 to Kaplitt, *et al.* (hereinafter "Kaplitt"), and claims 1-13, 15 and 16 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,858,351 to Podsakoff *et al.* (hereinafter "Podsakoff").

The filing date of Kaplitt is Sept. 27, 1995. The filing date of Podsakoff is January 18, 1996.

Please find attached a declaration pursuant to 37 C.F.R. § 1.131 by Dr. Geary, co-inventor of the present patent application (hereinafter "Geary Declaration 2"), stating that the invention date for the present invention was prior to September 27, 1995, and presenting evidence to that effect. Dr. Geary states, "The invention claimed in the subject application [09/938,200] was completed prior to September 27, 1995." Appended to the declaration are a research protocol detailing experiments using AAV vectors to transduce blood vessels in nonhuman primates that stated "AAV-based vectors will provide a means of direct and stable gene transfer into cells of the intact primate artery." (Geary Declaration 2, ¶ 3 and Exhibit A); a letter sent to Dr. Geary from Targeted Genetics Corporation detailing a Materials Transfer Agreement for the AAV vectors employed in initial animal experiments (Geary Declaration 2, ¶ 4 and Exhibit B); a letter to Dr. Geary from co-inventor Dr. Carmel M. Lynch documenting shipment to Dr. Geary of the AAV vectors for experiments performed in support of the invention (Geary Declaration 2, ¶ 5 and Exhibit C); photocopies of photomicrographs demonstrating expression of AAV viral vectors in endothelium of monkey blood vessels (Geary Declaration 2, ¶ 6 and Exhibit D); a copy of a laboratory notebook page of a technician in Dr. Geary's laboratory detailing the stain of blood vessels from confirmatory experiments (Geary Declaration 2, ¶ 6 and Exhibit E); and reference to the paper in which the confirmatory patterns of AAV expression were documented (Geary Declaration 2, ¶ 6).

Applicants respectfully request withdrawal of these rejections based on the above declaration, which establishes that the date of the present invention was prior to the filing date of both Kaplitt and Podsakoff, and therefore that Kaplitt and Podsakoff are not valid references under 35 U.S.C. § 102(e).

Rejections under 35 USC § 103(a)

Claims 1-16 stand rejected as allegedly being anticipated by U.S. Patent No. 5,851,521 to Branellec *et al.* (hereinafter "Branallec"), supported by U.S. Patent No. 5,328,470 to Nabel *et al.* (hereinafter "Nabel").

Applicants respectfully request that this rejection be withdrawn. Branellec is not a valid reference for 103 purposes, and Nabel standing alone does not support a rejection under 103(a).

Branellec does not qualify as a reference under any of the relevant sections of 35 U.S.C. 102, namely, 102(b), 102(a), and 102(e).

The issue date of Branellec is December 22, 1998, after the priority date of the instant application, March 4, 1996. Therefore Branellec does not qualify as a reference under 35 U.S.C. § 102(b).

The first U.S. filing date of Branellec is September 30, 1996. Therefore, Branellec does not qualify as a reference under 35 U.S.C. § 102(e). MPEP 2136.03 and *In re Hilmer*, 39 F. 2d 859 (CCPA 1966).

Branellec also does not qualify as a reference under 35 U.S.C. § 102(a), which requires that the invention be ". . . patented . . . in this or a foreign country, before the invention thereof by the applicant for patent." As stated above, the issue date of Branellec is December 22, 1998; in the U.S., the "date of patenting" is considered to be the issue date, and therefore the U.S. patent to Branellec does not qualify as a valid reference under 35 U.S.C. § 102(a).

Branellec claims priority to French Application No. 95/04234. The courts have held that an invention is not considered "patented" in France, for the purposes of 35 U.S.C. 102(a), until the date of delivery ("delivre") of the patent application. *Dulan Corp. vs. Deering Milliken, Inc.*, 353 F. Supp. 826, 832 (D.S.C., 1973) ("It affirmatively appears to this court that those inventor's exclusive rights which a patent envisions, accrued on the delivery (delivre) date."). *Ritter v. Rohm and Haas*, 271 F. Supp. 313, 317 (S.D.N.Y., 1967) ("There is no dispute that, in France,

all rights of a patentee accrue to him on the "delivre" date of his patent."). Concerning the "delivre" date, the court in Ritter stated:

> On that [the delivre] date, the Minster of Industry grants the application by signing a decree. Soon afterward the Patent Office notifies the applicant. As of the "delivre" date, the patentee acquires a monopoly right to exclude others, and he can sue for infringement. However, unlike American patents, French patents are not published on the same day they are granted. ***Ritter,*** 317.

About four weeks after the "delivre" date, the patent is published in the *Bulletin Officiel de la Propriete Industrielle* (BOPI). *Duplan*, p. 831. The Branallec patent was published in the BOPI on April 30, 1997. This is over a year after the priority date of the present application (March 4, 1996) and a year and a half after the latest possible date of invention according to the Geary Declaration 2 (September 27, 1995). Thus the "delivre" date of Branellec was approximately one year after the filing date of the present application and approximately one and one half years after the latest date of invention for the present application. Therefore, even the French patent to Branellec does not qualify as a reference under 35 U.S.C. § 102(a).

Because Branellec does not qualify as a reference under the relevant sections of 35 U.S.C. § 102, it is not a reference for the purposes of 35 U.S.C. § 103.

The Examiner relies on Nabel to cure deficiencies of Branellec. As discussed, Branellec is not a valid reference. Nabel, in itself, is insufficient to support a rejection under 35 U.S.C. § 103. The Examiner states that Nabel describes administering a viral vector to a blood vessel following balloon catheter injury results in delivery and expression in the adventitia. Applicants point out that Nabel teaches a catheter for use in delivering cells or other materials to the body of a subject. Nabel fails to teach, exemplify or suggest the use of rAAV vectors for transduction of cells in blood vessels. Thus, it lacks elements of Applicants' claims, nor does it contain any suggestion or motivation to provide the missing elements or any reasonable expectation of

success were the missing elements present. In short, Nabel alone does not provide a single one of the elements of a *prima facie* case of obviousness.

Because Branallec is not a valid reference and Nabel alone is insufficient to support a rejection under 35 U.S.C. § 103, Applicants respectfully request that this rejection be withdrawn.

Claims 1-16 stand rejected as being anticipated by Branellec in view of Kaplitt, as supported by Nabel.

Applicants respectfully request that this rejection be withdrawn. Branellec is not a valid reference for 103 purposes, as discussed above. Kaplitt is not a valid reference for 103 purposes for the reasons given above in answer to the rejection under 102 that relies on Kaplitt. Nabel standing alone does not support a rejection under 103(a), as detailed above. For these reasons, Applicants respectfully request that this rejection be withdrawn.

Double Patenting

Claim 11 is objected to under 37 C.F.R. 1.75 as being a substantial duplicate of claim 7. Claim 7 has been canceled.

CONCLUSION

Applicants have made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 226272001702.

Respectfully submitted,

Dated: March 10, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Replacement paragraph for the first paragraph on page 1:

--This application is a continuation of U.S. Serial No. 08/793,916, filed February 28, 1997, now abandoned, which is the U.S. National Phase of international application PCT/US97/03134, filed on February 28, 1997, which claims the benefit of U.S. provisional application 60/028,145 (converted from U.S. Serial No. 08/610,660), which was filed March 4, 1996.--

In the Claims:

1. (Amended) A method of transducing a cell in a blood vessel of an individual, comprising ~~introducing~~ contacting said cell with a recombinant adeno-associated viral (rAAV) vector ~~to a blood vessel of said individual~~ in vivo at a sufficient dosage and for a sufficient duration to transduce said cell, whereby said cell is transduced, and whereby a product of the nucleic acid of the rAAV is made.